APhA
American Pharmacists Association

The APhA Complete Review for the FPGEE

(Foreign Pharmacy Graduate Equivalency Examination), 2nd Edition

Corrections

Page 147

Question 14. There are numerous human clinical trials evaluating the potential efficacy of natural products in subjects with various ailments. Which of the following is true regarding evidence to support potential benefit of natural products?

Correction: It should state, "Which of the following is **NOT** true regarding evidence to support potential benefit of natural products?"

Page 146/148

Question 6. Which of the following has been shown to decrease digoxin serum concentrations?
A. *Panax ginseng*
B. *Panax quinquefolius*
C. *Eleutherococcus senticosus*
D. *Echinacea pallida*

There are 2 correct answers for this question, B & C.

Correction: B and C. *Panax quinquefolius* and *Eleutherococcus senticosus*, or Siberian ginseng, have been reported to decrease serum digoxin concentrations.

On page 351

The correct answer for 5 should be corrected to B with an edit to the explanation.

Correction: B. Experimental research designs include randomized controlled trials. Observational studies include cohort and case-control studies as well as retrospective epidemiologic studies.

Pages 342-343

Please see the edited pages on the subsequent pages, as the content has been reordered and organized.

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20-3 Introduction

Clinical research refers to studies conducted in humans seeking to answer a question regarding health care. It includes studies evaluating medical disease prevention, diagnosis, and treatment. Data derived from well-planned and well-executed clinical research studies are extremely important in advancing patient care. Although the basic principles of clinical research design techniques and processes are not particularly difficult to comprehend, actually conducting studies is a complex enough process that entire textbooks are devoted to trial design as well as to data processing and interpretation. Many health care practitioners lack the time and expertise to design and execute studies themselves without additional training, and practitioners may even be inadequately prepared to interpret published clinical data. Regardless, understanding the basics of clinical research design is essential for all practitioners to practice evidence-based medicine. Critical appraisal of medical literature and judicious use of new knowledge will aid clinicians in providing the best possible care to the patients they serve.

This chapter introduces the reader to the basic concepts of clinical research; clinical trial design, including the major types of clinical trials; and many of the key aspects of randomized controlled trials. The chapter also addresses the basic principles for evaluating the primary literature and the techniques for reviewing such data and implementing useful findings in clinical practice.

20-4 Fundamentals of Research Design and Methodology

There are two basic types of clinical research: observational research and experimental research. A brief description of each type follows:

- ***Observational research:*** In this type of research, the investigator observes what is occurring without intervening. Typically, descriptive statistics are used to summarize the study results. This method includes measures of central tendency (e.g., arithmetic mean, median, mode) and measures of variability (e.g., range, standard deviation, variance). Observational research may be retrospective or prospective. Retrospective studies involve looking back from the present, whereas prospective studies begin at the present time and observe study variables of interest from the present forward. One specific type of observational research that is very important within medicine is the case report. A case report retrospectively describes a specific clinical case or a limited number of cases. Case reports cannot establish a causal relationship but may often be the first evidence of a previously unknown or unrecognized relationship. Other observational clinical study designs are as follows:
  - ***Case series:*** This type of study is similar to a case report although it reports on a group of patients with similar clinical presentations or exposure to a particular treatment or condition compared with a single case or limited number of cases. A case series may be either retrospective or prospective. The lack of a control group and randomization limits the determination of a causal relationship and rigorous statistical analysis, respectively.
  - ***Cohort study:*** A cohort study selects participants on the basis of one or more specific characteristics and compares them over time to either a different set of patients or the rest of the general population that serves as the control group. In either case, the study group of interest is exposed to the test treatment or condition at the beginning of the evaluation period, whereas the other group is not exposed. Cohort studies are essentially the same as randomized controlled trials (discussed below) except for the absence of randomization. A cohort study can be conducted prospectively, in which case participants are selected on the basis of the study characteristics of interest and then observed following exposure until the conclusion of the study. Cohort studies can also identify

participants retrospectively, in which case participant records are used to identify and prospectively evaluate individuals with the selected characteristics thereafter. Yet another design is to study prospectively one group of patients possessing the study characteristics and having been exposed to the test treatment and to compare that group to a historical participant group evaluated retrospectively. A well-designed cohort study can provide convincing evidence of an association between study variables. However, the inability to randomize patients to one group or another is a major source of bias inherent in conducting cohort studies because the participant groups may not be comparable. *Bias* denotes systematic error within clinical investigations. Bias is distinct from *confounding variables*. The latter term is used to describe variables that are not systematically introduced into the study but that may affect the outcome of interest in clinical studies. Generally speaking, confounding variables cannot be controlled in clinical studies completely (e.g., use of concurrent medications during the course of a study).

- ***Case-control study:*** Case-control studies are similar to cohort studies in that one group of participants has a disease and is compared to a control group that does not have the disease. However, a best attempt is made to find patients within the control group who match the participants with the disease or condition on the basis of a predefined set of characteristics such as age or sex. Another difference is that case-control studies are always retrospective.

- ***Experimental research:*** In this type of research, a specific intervention or exposure to a condition is evaluated in a study group and typically compared with a control group. Experimental research is usually prospective in nature but it may use historical controls or controls from medical literature for the comparator group. Familiarity with the terminology of experimental clinical study designs is useful from several vantage points. One aspect is the ability to efficiently plan and conduct clinical research on the basis of accepted methodologies by motivated investigators. Perhaps more important for most clinicians is the ability to interpret medical literature as previously noted. Upon identification of the methodology used within a published study, the clinician should be able to readily conceptualize how a study was conducted.
  - ***Randomized controlled trial (RCT):*** In this type of trial, study participants are prospectively assigned randomly to one or more treatment or control groups upon meeting the inclusion criteria for the study. A well-designed and well-executed RCT provides evidence of a causal relationship between the intervention being investigated and the primary study outcome. The two most common design subtypes of RCTs are known as parallel and crossover.
    - ***Parallel RCT:*** In this study design, participants are randomized to one of the treatment or control arms of the study. Control groups may receive standard treatments, no treatment, usual care, or placebos. *Placebos* are inactive substances that are often used in clinical drug studies. Typically, study participants receive the assigned treatment or control for the entire trial in a parallel RCT (see Figure 20-1). Outcome responses for each treatment or control group are then compared at the conclusion of the study *between* patients assigned to each study group. Conditions being evaluated can be acute or chronic, which is one of the reasons that parallel RCTs are the most common prospective RCT design.
    - ***Crossover RCT:*** In this design, the study participants receive one or more of the treatments or controls for a predefined period during the course of the study. Participants are then switched or "crossed over" to one or more of the other treatment or control arms (see Figure 20-2). In this instance, outcome responses are compared *within* the same participants, resulting typically in less variability. Although crossover RCTs are efficient for evaluating causal effects of one treatment over another treatment within the same participant, a major limitation is that only stable, chronic, or episodic conditions can be studied. Examples of such conditions include glaucoma, epilepsy, and migraines. Even with chronic or episodic conditions, however, a return to the same baseline state is needed to use a crossover design. This return frequently requires a period of no treatment or usual treatment between study periods to avoid a carryover or residual effect as one treatment ends and the next one begins. This time period is referred to as a "washout" period.